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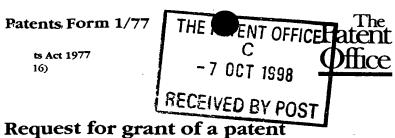
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		Gwent NP9 1RH
Your reference	P22412/LXM/BOU	
Patent application number (The Patent Office will fill in this part)	9821736.7	-7 OCT 1998
Full name, address and postcode of the or of each applicant (underline all surnames)	Giltech Limited 12 North Harbour Estate AYR KA8 8AA	
Patents ADP number (if you know it)		
If the applicant is a corporate body, give the	4013822001	60
country/state of its incorporation	United Kingdom	J.
Title of the invention	"Alginate Foam"	
Name of your agent (if you have one)	Murgitroyd & Company	
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	373 Scotland Street GLASGOW G5 8QA	
Patents ADP number (if you know it)	1198013	٠.,
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1
      FOAM
 2
 3
      The present invention is concerned with a foamable
 4
      formulation and the foam formed therefrom.
 5
     A wide variety of gels, creams, ointments, lotions and
 6
      other formulations are available for application to a
 7
                     The exact content of these compositions
      body surface.
 8
     will vary depending upon the purpose of application.
 9
      For example, a formulation may be applied to clean a
10
     body surface, to promote healing of any wound or
11
      injury, to prevent an exposed wound on the body from
12
      drying out, to prevent infection, etc.
                                               In certain
13
      circumstances the composition may include an active
14
15
      ingredient.
16
      In our International Patent Application published 13
17
      June 1996 under No WO-A-96/17595 we describe a foamable
18
      formulation which comprises a foamable carrier or
19
      gelling agent, for example an alginate gel, and an
20
      active ingredient, such as a water soluble glass
21
22
     powder.
23
24
      The product described in WO-A-96/17595 represented a
      considerable advance over the use of gel or cream.
25
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1 We have now found that by including a precipitant for 2 the gelling agent, in a slow-release form within the 3 composition, further improvements with regard to the 4 setting time of the foam and its stability can be 5 In particular, the added stability enables a 6 pre-foamed pad to be sterilised by irradiation or other 7 conventional means. 8 9 Thus, the present invention provides a formulation 10 comprising a foamed gelling agent admixed with a slowrelease precipitant therefor. The gelling agent may be 11 12 any agent capable of forming a foam, although preferably the gelling agent is physiologically 13 14 compatible and non-irritant when maintained in contact 15 with the body surface. The gelling agent may be a gel, 16 for example a sodium alginate gel, carageenan gel, 17 sodium carboxymethylcellulose gel or mixtures thereof. 18 19 20 The precipitant is desirably intimately admixed 21 throughout the whole of the foamed gelling agent, 22 preferably during the foaming process. In certain 23 circumstances however the presence of the precipitant 24 on one surface of the foamed gelling agent may be 25 sufficient to cause stabilisation of the foam. 26 Examples of precipitants include stabilising 27 crosslinking agents which render the gelling agent 28 insoluble. Examples include polyvalent metal ions of calcium, zinc, copper, silver or aluminium as well as 29 30 borates, glyoxal and amino-formaldehyde precondensates. 31 The role of the precipitant is to stabilise the foamed 32 33 gel so that a stable foam is produced. Generally, the 34 stable foam should be produced within a reasonable time 35 period since if the precipitant is too slow-acting, the 36 foam structure will have collapsed prior to

However, a very fast acting precipitant stabilisation. 1 may not allow sufficient time for the admixed gel to be 2 Desirably, the precipitant stabilises the gel 3 over a time period of 1 minute to 120 minutes, preferably within 30 minutes. The solubility of the 5 precipitant and hence the setting time of the foam may 6 7 be varied by adjusting the pH of the composition especially where the precipitant is based upon a 8 Generally, the solubility of a calcium 9 calcium salt. salt will be increased by lowering the pH. 10 adjusters include organic acids such as acetic, adipic, 11 citric, fumeric, lactic and tartaric acids. 12 13 Suitable precipitants include calcium citrate, calcium 14 carbonate, calcium phosphate, calcium hydrogen phospate 15 (CaHPO4), barium carbonate, barium phosphate, barium 16 sulphate, barium chloride and zinc carbonate. 17 18 Where the gelling agent comprises an alginate gel, a 19 carageenan gel or a carboxymethylcellulose gel one 20 preferred precipitant is a calcium salt. 21 calcium citrate has been used in the examples, other 22 slowly dissolving calcium salts are also suitable. 23 24 Where the gelling agent comprises 25 carboxymethylcellulose gel one preferred precipitant is 26 an aluminium salt. 27 28 In one embodiment the gelling agent and precipitant are 29 packaged separately and only admixed during the foaming 30 process or subsequent to foaming. 31 32 Optionally, the formulation may comprise other 33 additives such as decompactants which promote the 34 35 desired foam structure or other foaming agents,

plasticisers, humectants, preservatives, additives,

sequestering agents or active ingredients such as 1 2 antimicrobial agents, growth factors, hormones, living 3 cells, etc. 4 5 The foam may be applied directly to the body area and 6 allowed to produce a stable foam protective cover, for 7 example over a wound. 8 9 Alternatively, the foam can be produced onto a mould or 10 other surface area, allowed to cure and then applied to 11 the body surface. Optionally, the foam may be applied 12 about a substrate (for example cloth, mesh, non-woven pad of alginate fibres, nylon, rayon, polylactid acid, 13 14 polyglycolic acid, polycaprolactone or biocompatible glass fibres) which are then integrated into the foam 15 16 pad produced. 17 As an example, the foam may be used to treat 18 19 dermatological conditions (including psoriasis, atopic 20 and allergic eczema). It may be convenient in this 21 embodiment for the foam to deliver an active ingredient 22 normally used to alleviate such conditions, for example 23 a steroid such as hydrocortisone. 24 25 In another embodiment the foam may be used to treat 26 burns or scalds, including sunburn. 27 28 In another embodiment the foam may be applied 29 cosmetically, and for example may include skin 30 moisturising agents, nutritional agents and growth .31 factors suitable to promote skin regeneration. 32 intended for cosmetic use may include colorants or 33 pigments so that the foam may be applied to the skin as

34 35 36

The foam may be used prophylactically. In particular a

a cosmetic or to disguise any blemishes in the skin.

foam containing a UV blocking agent may be applied to 1 2 exposed areas of the skin to protect it from the effects of the sun. 3 4 The formulation of the invention is applied to the body 5 site of interest in the form of a foam and it is 6 7 therefore essential that the composition undergoes a foaming process before application to the body. 8 9 foaming process gas is forced into or is formed within the formulation to entrap small bubbles of gas therein, 10 11 thereby forming the foam. Any suitably gas or gas producing system can be used to produce the foam. 12 13 Mention may be made of butane and nitrous oxide, but other gases like air, nitrogen, hydrofluorocarbons such 14 as HFC134a or 227, hydrocarbons like propane, 15 16 isopropane or a mixture thereof, are also suitable. 17 Conveniently the foam may be produced by conventional means such as by using aerosol technology. 18 19 The formulation according to the present invention may 20 be stored in any convenient container until required. 21 22 Generally, the container will be designed to preserve 23 the sterile nature of the formulation. Conveniently the container will be provided with means to foam the 24 composition when required. Details are given in WO-A-25 26 96/17595. 27 28 Generally, the foam will be produced from sterile 29 ingredients. 30 Prior to the foaming process, the foamable carrier is 31 32 preferably in the form of a gel. The gel may be 33 sterilised and this is generally desirable where the 34 foam is intended for medical use. Usually, 35 sterilisation will take place by autoclaving the

formulation, since this is currently the most economic

means of achieving sterilisation. Autoclaving at 1 temperatures of from 100°C to 125°C for under 1/2 hour is 2 normally sufficient. Generally, the autoclaving 3 process should be as mild as possible, whilst being 4 sufficient to sterilise the formulation. For example, 5 autoclaving at temperatures of about 121°C for 15-20 6 minutes is acceptable. The autoclaved formulation may 7 then be foamed when cool. It is also possible, 8 however, to sterilise the formulation by other means, 9 for example by  $\gamma$ -irradiation or e-beam irradiation. 10 has been found that autoclaving the gel may cause the 11 MW of the foamable carrier to be slightly reduced. 12 Consequently it may be desirable to select a foamable 13 14 carrier having a higher MW than that ultimately required. 15 16 The foam forms an air-tight cover around any wound or 17 injury to which it is applied, and this prevents that 18 area from drying out and may also combat infection. 19 The advantages of applying a topical product in the 20 form of a foam include: 21 22 Easy rapid application, 23 1. 2. Conforms to surface irregularities, 24 Insulates the wound, 25 3. Cools the tissues, 4. 26 Offers antibacterial action to prevent 27 5. infection, 28 Biocompatibility with tissue, 29 6. Suitable for use as a vehicle for the 30 7. administration of pharmaceutical agents, 31 and/or 32 33 8. Maintains a moist environment. 34

35 Generally, the formulation of the present invention 36 will be applied directly to the body site of interest

in the form of a foam, the foam being produced from any 1 suitabl device (such as an aerosol) immediately before 2 It is, however, possible for a quantity application. 3 of the foamed formulation to be produced and then 4 applied onto the body site by any suitable means, for 5 example by hand or by spatula. This method may be 6 required for wounds having a narrow opening. 7

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As stated above, the foam may also be produced on a suitable surface and then dried to produce the foam sheet described above. Generally, the production of 11 the sheet will take place under sterile conditions or 12 may be sterilised after production. In the prior 13 described foam product of WO-A-96/17595, it was not 14 possible to provide a foamed pad product and then 15 sterilise the pad by conventional means such as  $\gamma-$ 16 irradiation, since it was found that the foam structure 17 deterioriated during sterilisation. With the inclusion 18 of the precipitant however, sterilisation of the 19 pad is possible both by  $\gamma$ -iradiation, ethylene oxide 20 sterilisation or other conventional means. 21 represents a very considerable advantage over the prior 22 Optionally the manufacture of a art product. 23 prefoamed product may envisage a continuous foaming 24 The sheet may be divided into a convenient 25 size and may be packaged. Optionally the foam sheet 26 may be produced on contoured surface so that it is 27 moulded to a pre-determined shape. 28

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Examples of suitable foamable carriers for use in the composition of the present invention include (but are not limited to) alginate and derivatives thereof, carboxymethylcellulose and derivatives thereof, collagen, polysaccharides (including, for example, dextran, dextran derivatives, pectin, starch, modified starches such as starches having additional carboxyl

and/or carboxamide groups and/or having hydrophillic 1 side-chains, cellulose and derivatives thereof), agar 2 and derivatives thereof (such as agar stabilised with 3 polyacrylamide), carageenan, polyethylene oxides, 4 glycol methacrylates, gelatin, gums such as xanthum, 5 guar, karaya, gellan, arabic, tragacanth and locust 6 Also suitable are the salts of the 7 bean gum. aforementioned carriers, for example, sodium alginate. 8 Mixtures of any of the aforementioned carriers may also 9 be used, as required. - 10 11 Preferred foamable carriers include alginate, 12 13 carageenan, carboxymethylcellulose, the derivatives and salts thereof and mixtures of any of these. 14 (the derivatives or salts thereof, such as sodium and 15 calcium alginate) are especially preferred. 16 carriers having a molecular weight of from 10,000 to 17 200,000 kDa are preferred, especially over 100,000 kDa, 18 for example 150,000 to 200,000 kDa, may be used. 19 20 The formulation may further comprise a foaming agent, 21 which promotes the formation of the foam. 22 having a surfactant character may be used. The 23 surfactants may be cationic, non-ionic or anionic. 24 25 Examples of suitable foaming agents include cetrimide, lecithin, soaps, silicones and the like. Commercially 26 available surfactants such as Tween™ are also suitable. 27 Cetrimide (which additionally has an anti-bacterial 28 activity) is especially preferred. 29 30 The formulation of the present invention (and thus the 31 foam) may be used to deliver pharmaceutically active 32 agents, in particular to deliver such agents in a 33 controlled release manner. Mention may be made of: 34

1	such as Chlorhexidine, acetic acid, polynoxylin,
2	povidone iodine, mercurochrome phenoxyethanol,
3	acridene, silver nitrate, dyes eg brilliant green,
4	undecanoic acid, silver sulphadiazine, silver
5	proteins and other silver compounds,
6	metronidazole, benzaclonium chloride;
7	
8	Nutritional agents, such as vitamins and proteins;
9	
10	Growth factors and healing agents, including
11	Ketanserin a serotonomic blocking agent;
12	
13	Living Cells;
14	
15	Enzymes include streptokinase and streptodormase;
16	·
17	<pre>Elements - zinc, selenium, cerium, copper,</pre>
18	manganese, cobalt, boron, arsenic, chromium
19	silver, gold, gallium;
20	
21	<pre>Charcoal;</pre>
22	
23	Desloughing and Debriding agents such as
24	hypochlorite and hydrogen peroxide;
25	
26	Astringents including potassium permanganate;
27	
28	Antibiotics exemplified by neomycin and framycetin
29	sulphate, sulfamylon, fusidic acid, mupirocin,
30	bacitracin, gramicidin.
31	
32	In addition the formulation of the present invention
33	may further comprise other conventional additives such
34	as plasticisers and humectants (such as glycerol,
35	propan -1,2-diol, polypropylene glycol and other
36	nolyhydric alcohols), free radical scay ngers to

1 stabilise against the effects of sterilisation by 2 irradiation, viscosity-adjusting agents, dyes and **3** · colorants, and the like. 4 Several experiments including comparatives tests have 5 been achieved by the Applicant in order to demonstrate 6 7 some of the advantages of the new compositions of the Of course the embodiments described 8 9 hereinbelow are submitted in order to better described 10 the invention and not to limit its scope. 11 12 13 EXAMPLE 1 PROCEDURE FOR MANUFACTURE OF UNIT BATCH (100 g) of 14 15 ALGINATE GEL 16 Typically the alginate gels are made according to the 17 18 following process: De-ionised (DI) water is measured and poured 19 20 into mixing vessel 1. Desired amounts of suitable alginate (for 21 2. example Keltone) and glycerine are weighed 22 using a calibrated balance, reading to 2 23 24 decimal places. 25 Alginate and glycerine are mixed together in a 3. 26 beaker until no lumps remain. 27 The whole alginate/glycerine mix is added very 4. 28 slowly to the water. 29 Once all the alginate/glycerine has been added to 5. 30 the water, the mixture is stirred until a smooth 31 gel has formed. 32 Several different alginate gels have been made 33 34 according the above process. They differ and are referred to by the amount of alginate (for example 35

Keltone) used. For example the alginate gel code 64 has

## the following composition:

2	GEL CODE	6 <del>,</del> 7
3	DI Water	80 ml
4	Glycerine	25.22 g
5	Keltone	6.5 g
6	Unit Batch Wt	111.72 g

The above composition can be varied to include other weights of alginate, which would be reflected in the gel code number. For example a composition having 8g alginate (plus 80ml DI water and 25.22g glycerine) would have gel code 8. Analogous gel codes are used when other gel formers (eg carageenan or CMC) are substituted for the alginate in the above composition.

### PROCEDURE FOR FOAM PRODUCTION

The propellant used to produce the foam can be compressed gases such as air, nitrogen, nitrous oxide or air, hydrofluorocarbons such HFC134a or 227 or hydrocarbons including propane, isopropane, n-butane, isobutane and 2-methylbutane.

Propellant vapour pressure can range from 0 to 110 PSIG at 70°C although the preferred range is 20 to 70 PSIG. Values within this range can be achieved for example by blending the three hydrocarbons propane, isobutane and butane. Calor Aerosol Propellants (CAP) sold by Calor Gas Ltd Slough may be used as propellant gas, when a blend of propane, isobutane and butane is used the proportions can be as follows:

1	<u>Grade</u>	Propane %	Isobutane %	n Butane%
2	CAP 30	11	29	60
3	CAP 40	22	24	54
4	CAP 70	55	15	30
5				
6	A foam a	ccording to	the invention	can advanta
7	produced	following t	the following	process.

- ageously be produced following the following process:
- 8 1. 100 g of a gel according to the invention is poured to an aerosol cannister. 9
- 2.5 g of calcium citrate (food grade) is 10 2. added to the cannister. 11
- A valve is crimped onto the cannister. 12 3.
- 13 4. Air is purged from the cannister.
- 4.5 g of propellant gas is added into the 14 5.
- cannister (65:35 CAP 40 : Isopentane 15
- propellant) and an actuator is positioned on 16
- the valve. 17
- The cannister is shaken vigorously for 20-30 18 6. 19 seconds.
- 20 the cannister is inverted and the foam dispensed. 7.

21

#### 22 EXAMPLE 2

- 23 Using a range of water-based gel formulations detailed
- below tests were done to improve the "setting" time and 24
- 25 stability of the gel and its foam.

26

- 27 Preferred alginate compositions have an amount of
- 28 Keltone ranging from 5-9g in the composition set out in
- 29 Example 1.

30

- 31 Experiment 1. Gel Code 63 Alginate gel and foam mixed
- with calcium citrate compared to Gel Code 6% alginate 32
- 33 gel alone

- 35 Foamed gel with calcium citrate
- 36 2.5 g calcium citrate was added to 100 g of gel and the

- 1 foamed gel was spread out onto plastic sheeting. The 2 resultant foam pad was liftable in 15 minutes. 3 4 Foamed gel without calcium citrate The above experiment was reproduced by foaming the gel . 5 on its own as described above. The "setting" time of 6 7 the foam was 10 hours. 8 9 The experiments were repeated using 100 g unfoamed gel with and without calcium citrate. Similar setting 10 times to those observed for the foamed gels were 11 obtained (15 minutes and 10 hours respectively) before 12 13 the gel pads were liftable. 14 15 Conclusion: Calcium citrate speeds up and controls the setting time of the gel and the foam. 16 17 18 Experiment 2. Gel Code 8 Alginate gel mixed with water 19 soluble glass (WSG) containing phosphate and boron 20 compared to gel code 8 alginate gel alone. 21 22 The WSG was comprised as follows: 23 28.5M% CaO 24 3M% Ag 25  $5M% B_2O_3$ 26 18.5M% MgO 27 45M% P205 28 29 Foamed gel with WSG 30 2.5 g of WSG was mixed with 100 g gel and the foamed mixture was spread out onto plastic sheeting. 31 32 resultant foam pad was liftable in 120 mins. 33 34 Foamed gel without WSG
- 36 its own. The "setting" time of the foam was

The above experiment was repeated by foaming the gel on

1 approximately 10 hours. 2 3 The experiments were repeated using 100 g unfoamed gel 4 with and without WSG. Similar setting times to those 5 observed for the foamed gels were obtained (120 minutes and 10 hours respectively) before the gel pads were 6 7 liftable. 9 WSG speeds up and controls the setting Conclusion: 10 time of the gel and the foam. 11 12 Experiment 3. Gel Code 4 Carageenan gel mixed with 13 calcium citrate compared to gel code 4 gel alone 14 15 Foamed gel with calcium citrate 3 q of calcium citrate was mixed with 100 g gel and the 16 17 foamed mix was spread out onto plastic sheeting. 18 resultant foam pad was liftable in 120 mins. 19 20 Foamed gel without calcium citrate 21 The above experiment was repeated by foaming gel on its 22 own as described above. The "setting" time of the foam 23 was 10 hours. 24 25 The experiments were repeated using 100 g unfoamed gel 26 with and without calcium citrate. Similar setting 27 times to those observed for the foamed gels were 28 obtained (120 minutes and 10 hours respectively) before 29 the gel pads were liftable. 30 31 Experiment 4. Gel Code 44 Carageenan gel and gel code 32 64 alginate gel mixed with calcium citrate compared to 33 gel code 4½ carageenan gel and gel code 6½ alginate gel 34 alone

1 2 Foamed gel with calcium citrate 2.5 q of calcium citrate was mixed with (50 q alginate 3 and 50 g carageenan) gel and the foamed mix was spread 4 out onto plastic sheeting. The resultant foam pad was 5 6 liftable in 15 mins. 7 8 Foamed gel without calcium citrate The above experiment was repeated by foaming the mixed 9 10 gel on its own. The "setting" time of the foam pad was 11 10 hours. 12 The experiments were repeated using 100 g unfoamed gel 13 14 with and without calcium citrate. Similar setting times to these observed for the foamed gels were 15 obtained (120 minutes and 10 hours respectively) before 16 17 the gel pads were liftable. 18 19 Experiment 5. Gel Code 64 Alginate gel mixed with 20 calcium citrate and added bentone IPM gel 21 22 2.5 g calcium citrate was added to 100 g of gel with 1g 23 bentone IPM gel, admixed in an aerosol cannister and 24 dispensed therefrom as a foam onto a plastic surface. 25 The resultant foam pad was liftable in 12 minutes. 26 Bentone IPM gel is an admixture of isopropyl myristate, 27 sterealkonium hectorite and propylene carbonate. 28 29 Conclusion: Calcium citrate and bentone gel control the setting time of the foam. Bentone gel also acts as 30 31 a reological agent and assists in the smoothness of delivery from the can. 32

1 2 Experiment 6. Gel Code 64 Alginate gel mixed with calcium citrate and added cetrimide 3 4 2.5 g calcium citrate was added to 100 g of alginate 5 gel with 1g cetrimide in an aerosol cannister and 6 foamed onto a plastic surface. The resultant foam pad 7 was liftable in 15 minutes. 8 9 Calcium citrate speeds up the setting time 10 Conclusion: Cetrimide increases the cell structure of 11 of the foam. 12 the product. 13 Experiment 7. Gel Code 6 Alginate gel mixed with 14 calcium citrate and added Tween 20 15 16 2.5 g Calcium citrate was added to 100 g of alginate 17 gel with 1g Tween 20 and foamed onto a plastic surface. 18 The resultant foam pad was liftable in 12 minutes. 19 20 Conclusion: Calcium citrate speeds up the setting time 21 The additive Tween 20 gave a much smoother 22 of the gel. delivery and an airier foam. Tween 80, 60 and 40 were 23 also tried and all assisted in the delivery and product 24 cell structure. 25 26 Experiment 8. Gel Code 4 Carboxmethyl cellulose and gel 27 28 code 6½ alginate gel mixed with calcium citrate compared to the gel alone 29 30 2.5 g calcium citrate was added to (50 g CMC & 50 g 31 alginate gel) and then the mixture was foamed onto a 32 plastic surface. The resultant foam pad was liftable 33 The gel foamed on its own was liftable in 25 minutes. 34 overnight (approx. 10 hours). 35 36

Experiment 9. Gel Code 4 Carboxmethyl cellulose gel mixed with aluminium chloride compared with the gel alone

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2 g aluminium chloride was mixed with 100 g CMC gel.

The gel was spread onto a plastic surface. The
resultant gel was liftable instantly. The gel alone was
liftable overnight (approx. 10 hours).

8 9 10

Experiment 10. Gel Code 6 Alginate gel mixed with citric acid compared to gel code 6 alginate gel alone

11 12

2.5 g of citric acid was mixed with 100 g alginate gel and the mix was spread out onto plastic sheeting. The resultant gel pad was liftable in 120 mins. 100 g of the gel alone was spread onto plastic sheeting and the resultant pad was only liftable overnight (approx. 10 hours).

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Experiment 11. Gel Code 6½ Alginate gel was mixed with the following powders on a 100 g gel: 2.5 g powder basis

23	
24 25	
26 27	
28 29	

Powder	Results as a gel	Results as a foam
Calcium Chloride	Gel pad was formed instantly	Fast setting foam
Calcium Sulphate	Gel pad formed reasonably quickly	Foam set reasonably quickly
Aluminium Chloride	Gel pad formed instantly	Fast setting foam
Calcium Metaborate	Gel pad formed instantly	Fast setting foam

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Experiment 12. Setting performances of a foam of a gel code 6% alginate gel as a function of the amounts of calcium citrate.

Batch No	Amount of calcium citrate per 100 g gel	Result
DM02 210798	4 g	Not dispensed - set in can
DM03 210798	3 g	Very difficult to dispense. 9½ minutes to set.
DM04 210798	2.5 g	Easier to dispense than above. 18½ minutes to set
DM05 210798	2.25 g	Taking longer to set. 20 minutes.
DM02 200798	2 g	Setting time - 40 minutes

Experiment 13. Gel Code 6½ alginate gel with calcium vibrate and isopertrane.

100g gel code 6% alginate gel was admixed with varying amounts of calcium citrate (2 to 4g), added to isopentane and mixed thoroughly before being spread onto a glass sheet. The isopentane vaporises at ambient temperatures and boils off through the gel leaving a foam pad of similar consistency to those produced by dispersion from an aerosol can. After half-an-hour the foam pads were liftable.

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